PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 October 2000 (04.10.00)	
International application No. PCT/US00/00648	**Applicant's or agent's file reference** BAYER 15 WO
International filing date (day/month/year) 12 January 2000 (12.01.00)	**Priority date** (day/month/year) 13 January 1999 (13.01.99)
Applicant RIEDL, Bernd et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   10 August 2000 (10.08.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Zakaria EL KHODARY
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
BAYER 15 WO		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US00/00648	12 JANUARY 2000	13 JANUARY 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant BAYER CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets.

   [1] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   I [X] Basis of the report

   II [ ] Priority

   III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV [X] Lack of unity of invention

   V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI [ ] Certain documents cited

   VII [ ] Certain defects in the international application

   VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10 AUGUST 2000	25 SEPTEMBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer ALAN ROTMAN
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/00648

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:
pages (See Attached), as originally filed
pages _____, as amended (together with any statement) under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos: NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- [ ] restricted the claims.
- [ ] paid additional fees.
- [X] paid additional fees under protest.
- [ ] neither restricted nor paid additional fees.

2. [ ] This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- [ ] complied with.
- [X] not complied with for the following reasons:

Please See Supplemental Sheet.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- [X] all parts.
- [ ] the parts relating to claims Nos. .

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/00648

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Inventive Step (IS)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Industrial Applicability (IA)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO

2. citations and explanations (Rule 70.7)

Claims 1-27,29,31-38,40,41,44,46,48-53,55-58 lack novelty under PCT Article 33(2) as being anticipated by Database HCaplus, DN 127:273945 DEARDEN J.C. et al. "Quantitative Structural Biodegradability studies: an investigation of the MITI aromatic compound database" especially RN# 24019-05-4

RN # 24019-05-4 reads on the compounds of the claimed invention wherein B is a an 6-membered substituted aryl , D is -NH-C(O)-NH-, A is a substituted moiety wherein L is a 6 membered ring directly linked to D and M is a bridging atom -O-, and L' is phenyl ring substituted by SO3H.

Claims 1-27,29,31-38,41,44,46,48-53,55-58 lack novelty under PCT Article 33(2) as being anticipated by Database HCAPLUS, DN 125:245169, BONWICK et al. "Production of Murine monoclonal antibodies against sulcofuron and flucofuran by in-vitro immunization" Abstract Journal of Immunological Methods, 1996, Vol. 196, No. 2, pages 163-173. See entire document, especially RN # 24019-05-04.

RN # 24019-05-04 reads on the compounds of the claimed invention wherein B is a an 6-membered substituted aryl , D is -NH-C(O)-NH-, A is a substituted moiety wherein L is a 6 membered ring directly linked to D and M is a bridging atom is -O-, and L' is a substituted phenyl group, substituted by "-SO3H"

Claims 1-27, 29, 31-38, 41, 44, 46, 48-53, 55-58 lack an inventive step under PCT Article 33(2) as being anticipated by Database HCaplus DN 126:166148 Winkler et al "Inhibitors of co-enzyme A-independent transacylase induce apoptosis in human HL-60 celles" See abstract Journal Of Pharmacol 1996, Vol. 279, No. 2, pages 956-966, RN # 162793-63-7 and 187173-03-1.

RN # 162793-63-7 and 187173-03-1 reads on the compounds of the (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C07D 211/78, 211/72; A61K 31/33, 31/54, 31/535, 31/17; C07C 275/20, 275/22, 275/24, 275/28 and US Cl.: 546/288, 289, 291, 300 ; 514/183, 222.2, 228.8, 588, 595, 597, 598; 564/49, 50, 52,

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-88, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) 89-102, 106-113, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Claim pages 103-105, filed with the letter of 25 September 2001.

This report has been drawn on the basis of the drawings,
page(s) NONE, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

IV. LACK OF UNITY OF INVENTION:

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2, and 13.3 is not complied with for the following reasons:

As applicant was previously notified this International Preliminary Examining Authority has found plural inventions claimed in the International Application covered by the claims indicated below:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional search fees must be paid.

Group I, claims 1-37, 50-58 and 60-67 in part, drawn to compounds pharmaceutical compositions and method of using these, wherein D is -NH-C(O)-NH-, B is a 3-tert butylphenyl or 5 tert butyl or trifluoromethyl (methoxy and / or chloro substituted) phenyl, and r is a non-hetero biaryl linked via an Oxygen atom.
Group II, claims 1-37, 50-58, 60-67 in part, drawn to compounds compositions and methods of using these, wherein D is -NH-C(O)-NH-, B is a 3-tert butylphenyl or a 5 tert butyl or trifluoromethyl (methoxy and/or chloro substituted) phenyl, and R is a biaryl, in which one of them is a pyridine group linked via an Oxygen atom.
Group III, claims 1-37 50-58, 60-67 in part, drawn to compounds pharmaceutical compositions and methods of using these, wherein D is -NH-C(O)-NH-, B is a 3-tert butylphenyl or a 5 tert butyl or trifluoromethyl (methoxy and /or chloro substituted) phenyl, and R is a biaryl, in which one of them is a pyrimidnyl linked via an Oxygen atom.
Group IV, claims 1-37, 50-58, 60-67 in part, drawn to compounds pharmaceutical compositions and method of using these, wherein D is -NH-C(O)-NH-, B is a 3-tert butylphenyl or a 5 tert butyl or trifluoromethyl (methoxy and /or chloro substituted) phenyl, and R is another hetero group linked via an Oxygen atom (may be subject to further restriction).
Group V, claims 1-37, 50-58, 60-67 in part, drawn to compounds, pharmaceutical compositions and a method of using these,

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

wherein R is a biaryl or an hetero group linked via an Nitrogen/amide/urea linkage and which may be subject to further restriction depending on the selected hetero group.
Group VI, claims 39, 42, 43, 45, 47, 49, 59 in part, drawn to a different scope of compounds and compositions, subject to further restriction.
Group VII, claims 38, 40, 41, 44, 46, 48, 49, 50 in part, drawn to a different scope of compounds of formula I, subject to further restriction.
Group VIII, claims 50-54, drawn to various salts of compounds and their compositions, maybe subject to further restriction.

and it considers that the International Application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

They form an improper Markush Grouping and do not have a common core.
1. The inventions listed as Groups I, II, and III do not relate to a single general inventive concept under PCT Rule 13. 1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
(f) "Markush Practice." The situation involving the so-called "Markush practice" wherein a single claim defines alternatives (chemical or non-chemical) is also governed by Rule 13.2.
(i) When the Markush grouping is for alternatives of chemical In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature. compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled: (A) all alternatives have a common property or activity, and (B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives, or (B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.
(ii) In paragraph (f)(i)(B)(1), above , the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of the existing prior art. The structural element may be a single component or a combination of individual components linked to-gether. The different A and D along with the L's, R's and M substituents have so many variables with the heterocyclic and non-hetero groupings, they have different bonding and properties, and have achieved a different status in the art, and is burdensome to search and hence are objected to as being drawn to an improper Markush group on the grounds of lack of a common nucleus. The terms A, B,L's, R's and M are so broad in scope that a prior art reference anticipating the claims with respect to one member under 35 USC 102(b) would not render obvious the same claims under 35 USC 103a with respect to another member. In view of the foregoing, restriction is required.

Applicants arguments in the response are not convincing. The common core is just the urea the rest of the groups "-L-(ML')" are all made up of variables from cyclic moieties , cyclic aryl or hetaryl moiety B. This large group of variable does not constitute a common core.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 1. REASONED STATEMENTS:
The report as to Novelty was positive (YES) with respect to claims 28,30,39,42,43,45,47,54,59-67.
The report as to Novelty was negative (NO) with respect to claims 1-27,29,31-38,40,41,44,46,48-53,55-58.
The report as to Inventive Step was positive (YES) with respect to claims NONE.
The report as to Inventive Step was negative (NO) with respect to claims 1-67.
The report as to Industrial Applicability was positive (YES) with respect to claims 1-67.
The report as to Industrial Applicability was negative (NO) with respect to claims NONE.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
claimed invention wherein B is a an 6-membered substituted aryl , D is -NH-C(O)-NH-, A is a substituted moiety wherein L is a 6 membered ring directly linked to D and M is a bridging atom -O-, and L' is a hetero-ring.

Claims 1-67 lack an inventive step under PCT Article 33(3) as being obvious over Database HCAPLUS DN 127:293717 **KURIK, M.V.** et al. and DN 127:34137, **KUBO** et al. and 126:166148 **WINKLER** et al, and DN 98:78152 CHUGAI Pharmaceutical Co., Ltd. Japan. and DN 127:273945 **DEARDEN** et al and DN 125: 245169 **BONWICK** et al.
The above references disclose compounds with a hetero or a phenyl, substituted or unsubstitued as an L' or L , M is a 1 or a 3 atom linker , D is a -NH-C(O)-NH- and B is an aryl.
All these various RN # discloses compounds with substituents similar to that of the claimed invention. These compounds are used in inhibiting raf kinase, and are cancerostatic (esp. leukemia) i.e., pharmaceutical uses. Thus one of ordinary skill in the art would have a reasonable expectation of success at using similar compounds with different acidic substituents on the L' substituents in view of DN 127:273945 Dearden J.C. et al "Quantitative Structural Biodegradability studies: an investigation of the MITI aromatic compound database " especially RN# 24019-05-4 and DN 125:245169, **BONWICK** et al. "Production of Murine monoclonal antibodies against sulcofuron and flucofuran by in-vitro immunization" Abstract, Journal of Immunological Methods. 1996, Vol. 196, No. 2, pages 163-173. See entire document, especially RN # 24019-05-04, for pharmaceutical uses.

Claims 1-67 meet the industrial applicability as defined by PCT Article 33(4).

---------- NEW CITATIONS ----------
NONE

39. A compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L^1)$_q$, where L is a substituted or unsubstituted phenyl or [peritoneal] pyridinyl moiety bound directly to D, L^1 comprises a substituted phenyl, [peritoneal] pyridinyl or pyrimidinyl moiety, M is a bridging group having at least one atom, q is an integer of from 1-3; and

B is a substituted or unsubstituted phenyl or [pyridine] pyridinyl group bound directly to D,

wherein L^1 is substituted by at least one substituent selected from the group consisting of [-SO_2R_x] -C(O)R_x and -C(NR_y) R_z,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo, and ;

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

-OSi(R_f)$_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which

optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is -C(O)-, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and Wn, where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NO_2$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is -O-, -S-, $-N(R^7)$-, $-(CH_2)_m$-, -C(O)-, -CH(OH)-, $-(CH_2)_mO$-, $-(CH_2)_mS$-, $-(CH_2)_mN(R^7)$-, $-O(CH_2)_m$- CHX^2-, $-CX^2_2$-, $-S-(CH_2)_m$- and $-N(R^7)(CH_2)_m$-, where m= 1-3, and X^2 is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is

independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-NO_2$, $-OR^7$, $-SR^7$ $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, and $-NR^7C(O)OR^7$; and

wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, $-N(R^7)-$, $-(CH_2)_m-$, -C(O)-, -CH(OH)-, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$ CHX^a-, $-CX^a_2-$, $-S(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where m= 1-3, X^a is halogen.

40. A compound as in claim 38 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by-OH.

41. A compound as in claim 38 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by a moiety having an ionizable hydrogen and a pKa of 10 or less.

42. A compound as in claim 39 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by-OH.

43. A compound as in claim 39 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by a moiety having an ionizable hydrogen and a pKa of 10 or less.

44. A compound as in claim 38 wherein substituents for B and L and additional substituents for L, are selected from the group consisting of C_1-C_{10} alkyl up to per halo substituted C_1-C_{10} alkyl, CN, OH, halogen, C_1-C_{10} alkoxy and up to per halo substituted C_1-C_{10} alkoxy.

45. A compound as in claim 39 wherein substituents for B and L and additional substituents for L, are selected from the group consisting of C_1-C_{10} alkyl up to per halo substituted C_1-C_{10} alkyl, CN, OH, halogen, C_1-C_{10} alkoxy and up to per halo substituted C_1-C_{10} alkoxy.

46. A compound of claim 38 wherein L^1 is substituted by $C(O)R_x$ or SO_2R_x.

47. A compound of claim 39 wherein L^1 is substituted by $C(O)R_x$.

48. A compound of claim 46 wherein R_x is NR_aR_b and R_a and R_b are independently hydrogen and a carbon based moiety of up to 30 carbon atoms optionally